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# Reactions of Ketene with Compounds Containing Active Methylene Group. (VII)<sup>1)</sup>

## On the Mechanisms of Reactions of Ketene with Compounds Containing an Active Methylene Group or with Phenols

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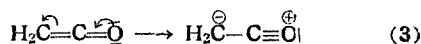
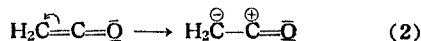
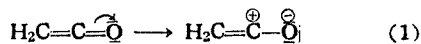
In previous papers of this series, experimental results of the reactions of ketene with compounds containing an active methylene group such as ethyl acetoacetate, acetylacetone, diethyl malonate and ethyl cyanoacetate, or with phenols such as phenol, resorcinol, phloroglucinol and dimedone, were shown.

When the reactions under ice-cooling or warming on a steam-bath were performed in various conditions, that is to say, without catalyst, using sodium salts of the abovementioned compounds or in the presence of sulfuric acid, pyridine or some other organic bases, the C-acetyl derivatives or the O-acetyl derivatives of them were obtained according to the reaction conditions.

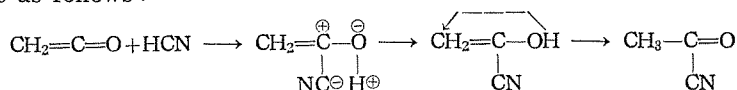
In this paper, these experimental results are summarized, and the reaction mechanisms of C-acetylation and O-acetylation with ketene are discussed.

Experimental results reported in parts I-IV<sup>2) 3) 4) 5)</sup> of this series are summarized in Table 1. Those in part V<sup>6)</sup> and part VI<sup>7)</sup> are shown in Table 2 and Table 3, respectively.

Canonical structures<sup>8) 9)</sup> of ketene are as follows:



Formula (1) has been used very often to explain the reactions of ketene. For example, the process of reaction of ketene with hydrogen cyanide ( $K_A = 4.79 \times 10^{-10}$ ,  $18^\circ\text{C}$ )<sup>10)</sup> is as follows:<sup>11)</sup>



In this reaction, ketene reacts as a base. From this point of view, in which ketene reacts as a base, reactions of ketene with compounds containing an active methylene group or with phenols will be considered.

\* 磯島 敏三

Table 1. Reactions of ketene with compounds containing an active methylene group.

Catalyst	React. Temp. <sup>1)</sup>	Compds. Cont. A. M. G		$\text{H}_2\text{C} \begin{matrix} \text{COCH}_3 \\ \text{COCH}_3 \end{matrix}$	$\text{H}_2\text{C} \begin{matrix} \text{COCH}_3 \\ \text{COOC}_2\text{H}_5 \end{matrix}$	$\text{H}_2\text{C} \begin{matrix} \text{COOC}_2\text{H}_5 \\ \text{COOC}_2\text{H}_5 \end{matrix}$	$\text{H}_2\text{C} \begin{matrix} \text{CN} \\ \text{COOC}_2\text{H}_5 \end{matrix}$
		Products					
None	Low	Name <sup>2) 3)</sup>		C	×	—	—
		Conv. ratio (%)		52			
		Yield <sup>4)</sup> (%) I.		31			
		II.		60			
	High	Name		C	C	×	×
		Conv. ratio (%)		76	43		
		Yield (%) I.		61	37		
		II.		80	86		
Na-salt <sup>5)</sup>	Low	Name		C	C	C	C
		Conv. ratio (%)		40	100	35	50
		Yield (%) I.		7	55	18	10
		II.		17	55	51	20
	High	Name		—	C	C	C
		Conv. ratio (%)			98	58	43
		Yield (%) I.			57	20	13
		II.			58	34	30
conc. H <sub>2</sub> SO <sub>4</sub>	Low	Name		O	×	—	—
		Conv. ratio (%)		40			
		Yield (%) I.		34			
		II.		85			
	High	Name		O	O	×	×
		Conv. ratio (%)		60	85		
		Yield (%) I.		22	67		
		II.		37	79		
Pyridine	Low	Name		O	O (rich) C (poor)	—	—
		Conv. ratio (%)		32	25		
		Yield (%) I.		22	25		
		II.		69	100		
	High	Name		O (rich) C (poor)	O (rich) C (poor)	C	C
		Conv. ratio (%)		48	52	20	19
		Yield (%) I.		28	40	4	9
		II.		59	77	20	47
Pyridine <sup>6)</sup> (eq. mol.)	Low	Name		O	O	—	—
		Conv. ratio (%)		60	39		
		Yield (%) I.		25	37		
		II.		42	95		
	High	Name		O	O	C	C
		Conv. ratio (%)		60	58	20	64
		Yield (%) I.		28	28	4	58
		II.		47	48	20	90

(1) Reaction temperature: Low—Cooling with ice (0–10°C);

High—Warming on a steam-bath (60–90°C).

(2) C: the C-acetyl derivative of the compound containing an active methylene group.

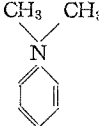



O: the O-acetyl derivative of the compound containing an active methylene group.

(3) ×: No reaction.

(4) Yield I: Yield based on the compound containing an active methylene group used.  
II: Theoretical yield.(5) Na-salt: Treated with 20% H<sub>2</sub>SO<sub>4</sub> after the reaction of ketene with the salt of the compound containing an active methylene group.

(6) Equimolar pyridine was used.

Table 2. Reactions of ketene with ethyl acetoacetate in the presence of some organic bases.

React. Temp. <sup>1)</sup>		Catalyst					$(C_2H_5)_3N$		$NH_4OH$	$NaOH$
		$K_B$		$2.4 \times 10^{-10}$	$3.2 \times 10^{-10}$	$1.2 \times 10^{-9}$	$5.3 \times 10^{-4}$	$1.6 \times 10^{-3}$	—	—
Low	O-acetyl der. <sup>2)</sup>	$\times^{4)}$	O (rich)	O (rich)	O (rich)	O (rich)	O (rich)	O (nearly equal amount)	$\times^{4)}$	C (only)
	C-acetyl der.		C (poor)	C (poor)	C (poor)	C (poor)	C (poor)	C (poor)		
	Conv. ratio (%)	—	42	9	32	91	48	—	—	94
	Yield <sup>3)</sup> (%)	I.	40	7	26	57	37	—	—	49
		II.	95	78	81	63	77	—	—	52
High	O-acetyl der.	C (only)	C (only)	C (only)	C (rich)	O (nearly equal amount)	C (only)	—	—	—
	C-acetyl der.				C (poor)					
	Conv. ratio (%)	43	89	60	52	72	71	—	—	—
	Yield (%)	I.	37	56	37	40	39	—	—	—
		II.	86	63	62	77	55	—	—	—

(1) Reaction Temperature: Low—Cooling with ice (0–10°C);  
High—Warming on a steam-bath (70–90°C).

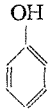
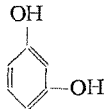
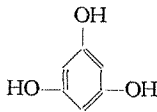
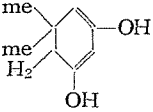

(2) O: the O-acetyl derivative of ethyl acetoacetate.  
C: the C-acetyl derivative of ethyl acetoacetate.

(3) Total yield of the O-acetyl derivative and the C-acetyl derivative:

I. Yield based on ethyl acetoacetate used.  
II. Theoretical yield.

(4) No reaction.

Table 3. Reactions of ketene with phenol, resorcinol, phloroglucinol and dimedone.

Catalyst	React. Temp. <sup>1)</sup>	Phenols Products				
None	Low	Name <sup>2) 3)</sup>	O	—	×	O*
		Yield <sup>4)</sup>	80			55
	High	Name	—	O (mono), O (di)	O (tri)	O*
		Yield		67, 98	2	72
Na <sup>5)</sup> Salt	Low	Name	O*	—	O (tri)	O*
		Yield	68		31	61
	High	Name	O*	O* (mono, di)	resine	O*
		Yield	74	78		61
H <sub>2</sub> SO <sub>4</sub>	Low	Name	O	—	resine	×
		Yield	85			
	High	Name	—	O (di)	resine	resine
		Yield		77		
 (eq. mol.) <sup>6)</sup>	Low	Name	O	—	O (tri)	×
		Yield	87		14	
	High	Name	—	O (di)	O (tri)	O*
		Yield		88	26	61
AcONa	Low	Name	—	—	—	×
		Yield				
	High	Name	—	—	—	O*
		Yield				44

(1) React. Temp. : Low—Cooling with ice or room temp. (solvent : ether).

High—Warming on a Steam-bath (solvent : benzene).

(2) O : the O-acetyl derivative.

O (mono) : the O-mono-acetyl derivative.

O (di) : the O-di-acetyl derivative.

O (tri) : the O-tri-acetyl derivative.

O\* : the O-acetyl derivative with a little of the C-acetyl derivative, which seems to be present although not confirmed.

(3) × : No reaction.

(4) Yield (%) : Theoretical yield.

(5) No-Salt : Treated with 20 % H<sub>2</sub>SO<sub>4</sub> after the reaction.

(6) Equimolar pyridine was used.

## (1) THE MECHANISMS OF REACTIONS WITHOUT CATALYST

Mechanisms of reactions without catalyst will be considered.

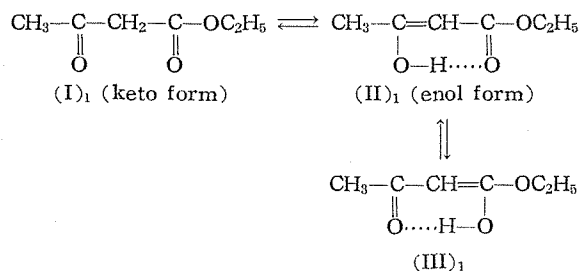
The  $PK_A$  values of the compounds used in the experiments are shown in Table 4.

Table 4. The  $PK_A$  values of the compounds used in the experiments.

Compounds	$PK_A$
Acetylacetone	9.3 <sup>12)</sup>
Ethyl acetoacetate	10.7 <sup>12)</sup>
Diethyl malonate	12.9 <sup>12)</sup>
Ethyl cyanoacetate	( $\geq 12.9$ )
Phenol	9.9 <sup>13)</sup>
Resorcinol	9.5 <sup>13)</sup>
Phloroglucinol	9.4 <sup>13)</sup>
Dimedone	5.2 <sup>13)</sup>

At first, to explain the mechanism of reactions of ketene with compounds containing an active methylene group without catalyst, for example, the reaction of ketene with ethyl acetoacetate will be considered.

Ethyl acetoacetate exhibits keto-enol tautomerism.<sup>14)</sup> The enol content at equilibrium (at 20°C) was 7.4 % according to the bromination method devised by K. H. Meyer.<sup>15)</sup> It was already proved by infrared spectrum<sup>16)</sup> that the enol form was stabilized by the following intramolecular hydrogen bond and conjugated system.



Therefore, when ketene is passed into ethyl acetoacetate, ketene does not react with the enol form which is stabilized to the extent of some 5–10 kcal./mole by the hydrogen bond<sup>17)</sup> and to the extent of some 2–3 Kcal./mole by the conjugated system,<sup>17)</sup> but reacts with the keto form which is more polar<sup>18)</sup> ( $PK_A = 10.7$ ) than the enol form, that is to say, has a stronger ionization tendency of C–H in the active methylene group.

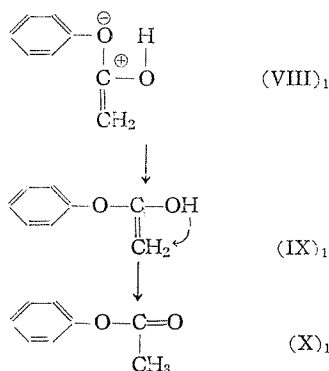
As soon as ketene takes a proton from the active methylene group, the formed carbonium cation combines with the carbanion (IV)<sub>1</sub> which is formed by loosing a proton, and through the intermediate (V)<sub>1</sub>, the C-acetyl derivative (VI)<sub>1</sub> of ethyl acetoacetate is obtained.

# 1h

(VI)  $\vdash$ 

(XXX)

# Reactions of Ketene with Active Methylene Compounds

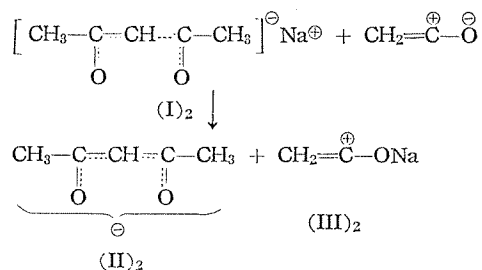


The O-acetyl derivatives of resorcinol, phloroglucinol and dimedone are respectively formed by the same mechanism as the O-acetyl derivative of phenol is formed.

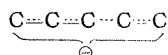
## (2) THE MECHANISMS OF REACTIONS OF KETENE WITH SODIUM SALTS OF COMPOUNDS CONTAINING AN ACTIVE METHYLENE GROUP OR WITH SODIUM SALTS OF PHENOLS

At first, to explain the mechanism of reactions of ketene with sodium salts of compounds containing an active methylene group, for example, the reaction of ketene with sodium salt of acetylacetone will be considered.

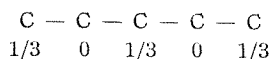
In the reaction of ketene with the sodium salt (I)<sub>2</sub> of acetylacetone, ketene takes a sodium cation from the salt and forms the carbonium cation (III)<sub>2</sub>. On the other hand, the negative ion (II)<sub>2</sub> is given by losing a sodium cation from the salt and it has a resonance system.



Next, the distribution of electron density in the negative ion (II)<sub>2</sub> will be considered. According to Yonezawa's calculation<sup>23)</sup> by the molecular orbital method, when a positive ion attacks the following resonance system,

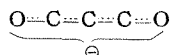


the distribution of electron density is as follows:

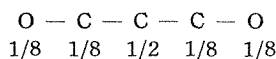




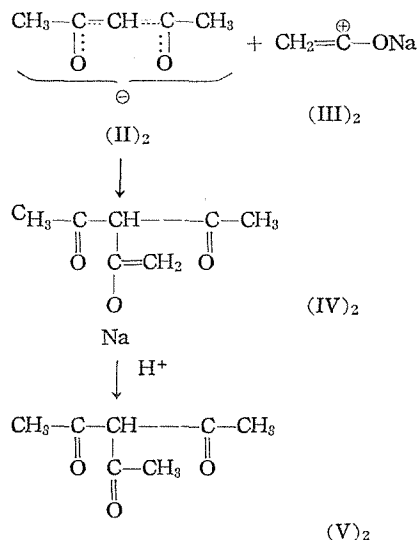
On the basis of this calculation, when a positive ion attacks the following resonance system in which both terminal carbons of the above resonance system are replaced with oxygens,



the distribution of electron density is as follows:



So, when a positive ion attacks the resonance system (II)<sub>2</sub>, the electron density at the carbon of active methylene group is much larger than at the oxygen in (II)<sub>2</sub>. Therefore, when the carbonium cation (III)<sub>2</sub> attacks (II)<sub>2</sub>, it combines with the carbon of the active methylene group of (II)<sub>2</sub>, and through the intermediate (IV)<sub>2</sub>, the C-acetyl derivative (V)<sub>2</sub> of acetylacetone is formed.



On the other hand, even if the carbonium cation (III)<sub>2</sub> combines with the oxygen in (II)<sub>2</sub> to give the O-acetyl derivative, its yield is very low.

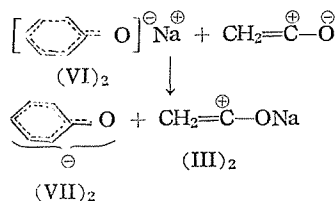
The formation of the C-acetyl derivatives of ethyl acetoacetate, diethyl malonate and ethyl cyanoacetate are respectively interpreted by the same mechanism as the C-acetyl derivative of acetylacetone is formed.

Next, to explain the mechanism of reactions of ketene with sodium salts of phenols, for example, the reaction of ketene with sodium salt of phenol will be considered.

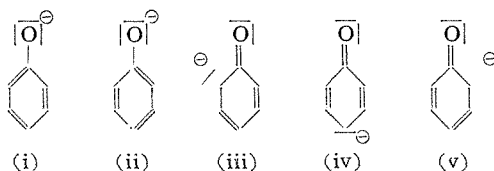
In the reaction of ketene with the sodium salt of phenol (VI)<sub>2</sub>, ketene takes a sodium cation from the salt, giving a carbonium cation (III)<sub>2</sub>. On the other hand,

# Reactions of Ketene with Active Methylene Compounds

the phenolate ion (VII)<sub>2</sub> which has been formed by loosing a sodium cation from the salt, has a resonance system.



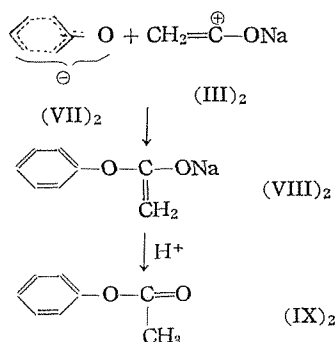
The canonical structures<sup>24)</sup> of this phenolate ion are as follows:



The resonance energy of this phenolate ion is about 8 Kcal./mole<sup>26)</sup> greater than that of phenol (39<sup>26)</sup> + 7<sup>27)</sup> = 46 Kcal./mole), therefore being 54 Kcal./mole.

Even if 15 Kcal./mole (54 Kcal./mole – 39 Kcal./mole) is quite due to the contribution of (iii), (iv) and (v) to the resonance, it is much smaller than the resonance energy of the benzene nucleus (39 Kcal./mole), so the contribution of (i) and (ii) to the resonance of the phenolate ion is very large.

Therefore, the electron density at oxygen is largest, and the carbonium cation (III)<sub>2</sub> does not combine with the carbon, but with the oxygen in (VII)<sub>2</sub>. Thus, through the intermediate (VIII)<sub>2</sub>, the O-acetyl derivative (IX)<sub>2</sub> of phenol is formed.



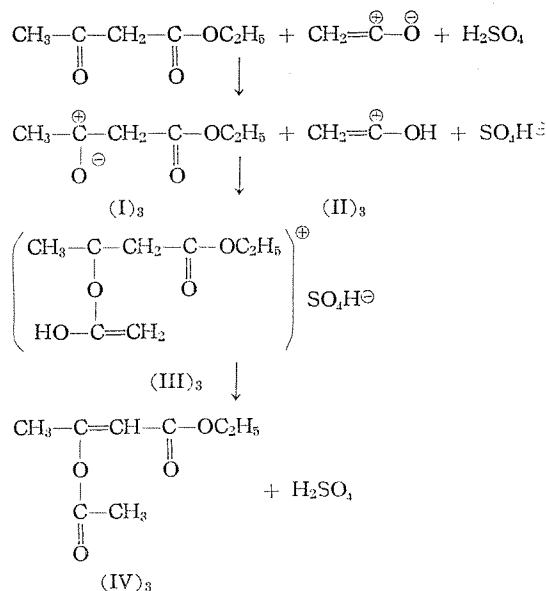
Even if (III)<sub>2</sub> combines with the carbon in (VII)<sub>2</sub>, only a little of the C-acetyl derivative is formed.

The O-acetyl derivatives of resorcinol, phloroglucinol and dimedone are respectively formed by the same mechanism as the O-acetyl derivative of phenol is formed.

## (3) THE MECHANISMS OF REACTIONS IN THE PRESENCE OF SULFURIC ACID

At first, to explain the mechanism of reactions of ketene with compounds containing an active methylene group in the presence of sulfuric acid, for example, the reaction of ketene with ethyl acetoacetate will be considered. When ketene is passed into ethyl acetoacetate to which sulfuric acid is added as a catalyst, a proton lost from sulfuric acid combines with the oxygen of the carbonyl group in ketene and the carbonium cation (II)<sub>3</sub> is formed.

On the other hand, although the proton has a possibility to combine with the oxygen of carbonyl group in ethyl acetoacetate, they do not combine because of the chelate ring formed by the hydrogen bond. Therefore, through the complex compound (III)<sub>3</sub> which is formed by the reaction of ethyl acetoacetate with the carbonium cation (II)<sub>3</sub>, the O-acetyl derivative (IV)<sub>3</sub> of ethyl acetoacetate is obtained. The above-mentioned reaction mechanism is shown in the following formulas:



The O-acetyl derivative of acetylacetone is formed by the same mechanism as the O-acetyl derivative of ethyl acetoacetate is formed.

While, even if the O-acetyl derivatives of diethyl malonate and ethyl cyanoacetate are formed respectively by the same mechanism as the above, they are too unstable to be detected.

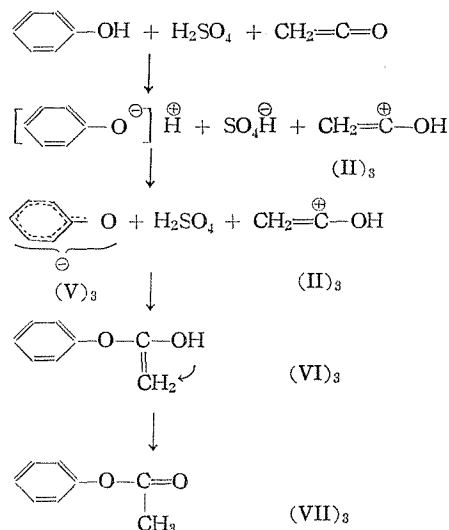
Then, to explain the mechanism of reactions of ketene with phenols in the presence of sulfuric acid, for example, the reaction of ketene with phenol will be considered.

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When ketene is passed into phenol to which sulfuric acid is added as a catalyst, ketene takes a proton from sulfuric acid, therefore the bisulfate anion and carbonium cation (II)<sub>3</sub> are formed respectively.

On the other hand, as phenol gives a proton to the bisulfate anion, the phenolate ion (V)<sub>3</sub> having a resonance system is formed. Then, the O-acetyl derivative of phenol is formed from (II)<sub>3</sub> and (V)<sub>3</sub>.

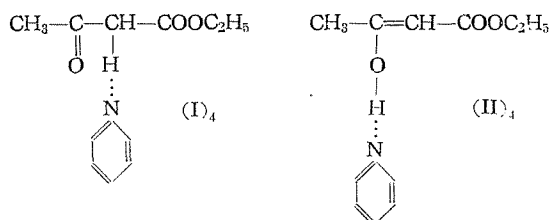
The above-mentioned mechanism is shown in the following formulas:



The O-acetyl derivatives of resorcinol are formed by the same mechanism as the O-acetyl derivative of phenol is formed.

#### (4) THE MECHANISMS OF REACTIONS IN THE PRESENCE OF PYRIDINE AND SOME OTHER ORGANIC BASES

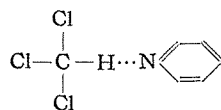
At first, to explain the mechanisms of reactions of ketene with compounds containing an active methylene group in the presence of pyridine, for example, the reaction of ketene with ethyl acetoacetate will be considered. In the mixture of ethyl acetoacetate and pyridine, the following hydrogen bonds, (I)<sub>4</sub> and (II)<sub>4</sub>, are presumed.



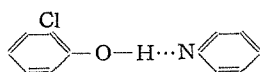
But the hydrogen bond (II)<sub>4</sub> was denied by Le Fèvre,<sup>28)</sup> because it was proved

by infrared spectrum that the enol content (4%)<sup>29)</sup> of ethyl acetoacetate in pyridine is nearly equal to that (7.4%) of pure ethyl acetoacetate.

While, in the mixture of chloroform and pyridine, the following hydrogen bond:



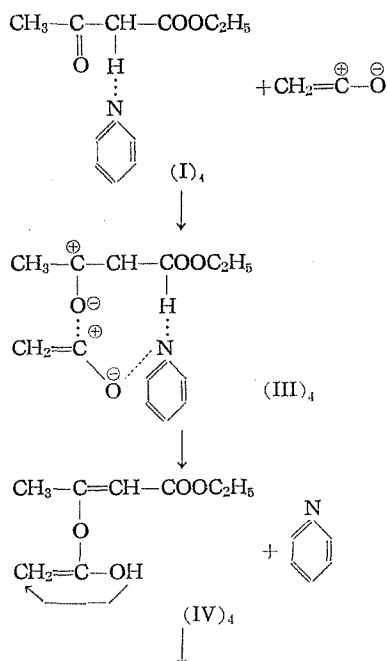
was proved by infrared spectrum<sup>30)</sup> or an addition compound presented by the freezing point-composition diagram.<sup>51)</sup> The following hydrogen bond between *o*-chlorophenol and pyridine was also proved by the freezing point-composition diagram,<sup>52)</sup>



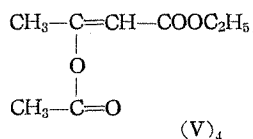
and moreover the  $\text{PK}_A$  value of *o*-chlorophenol (10.1)<sup>33)</sup> is nearly equal to the  $\text{PK}_A$  value of ethyl acetoacetate (10.7).

The above-mentioned results are sufficient to support the existence of the hydrogen bond (I)<sub>4</sub>.

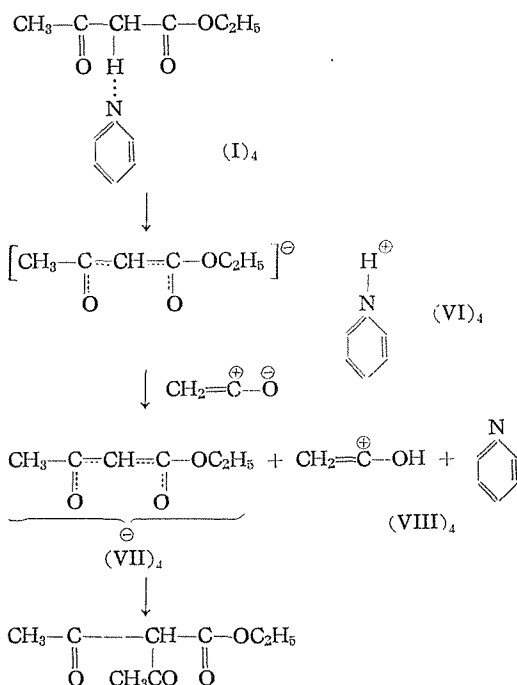
Therefore, the intermediate (III)<sub>4</sub> is formed from ketene and (I)<sub>4</sub>, and then after rearrangement of hydrogen in the intermediate (IV)<sub>4</sub> which is given from (III)<sub>4</sub>, the O-acetyl derivative of ethyl acetoacetate is obtained. The O-acetyl derivative of acetylacetone is formed by the same mechanism as the O-acetyl derivative of ethyl acetoacetate is formed.



# Reactions of Ketene with Active Methylene Compounds



On the other hand, some C-H fission of the active methylene group in (I)<sub>4</sub> occurs and a complex compound (VI)<sub>4</sub> is formed. The reaction of ketene with (VI)<sub>4</sub> gives an anion (VII)<sub>4</sub> and a cation (VIII)<sub>4</sub> from which a little of the C-acetyl derivative is obtained by the same mechanism as it is obtained from ketene and the sodium salt of ethyl acetoacetate.



The experimental results of reactions of ketene with ethyl acetoacetate in the presence of some organic bases are shown in Table 2. Hydrogen bonds corresponding to (I)<sub>4</sub> are formed between ethyl acetoacetate and some organic bases shown in Table 2 respectively. As they are stable at low temperatures, much of the O-acetyl derivative and a very little of the C-acetyl derivative are formed by the above-mentioned mechanisms. While, at high temperatures, the hydrogen bond between ethyl acetoacetate and dimethylaniline or quinoline is unstable and because of fission of the hydrogen bond, the C-acetyl derivative is formed by the same mechanism as in case of no catalyst.

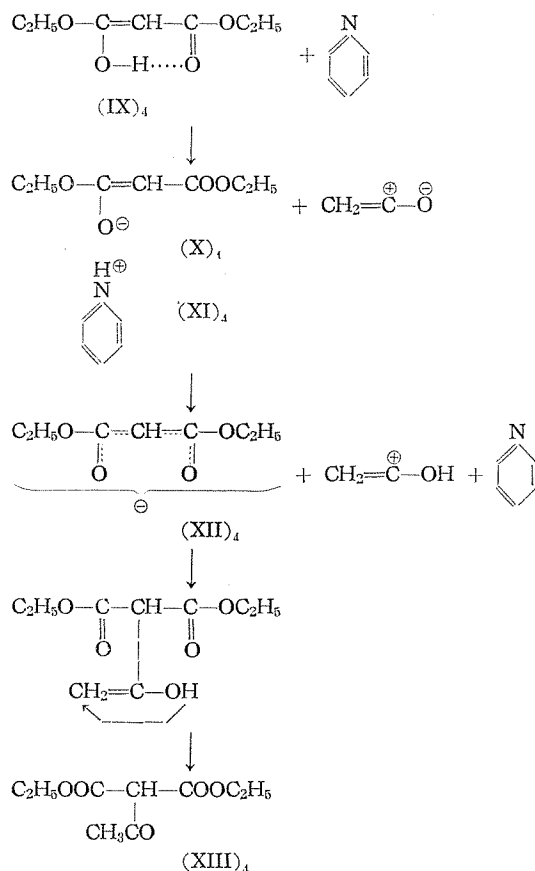
On the other hand, the stronger the basicity of the organic base (pyridine, triethyl amine, piperidine) is, the more the hydrogen bond corresponding to (I)<sub>4</sub> decreases and also the more the dissociation corresponding to (IV)<sub>4</sub> increases, and

therefore the more the C-acetyl derivative is formed.

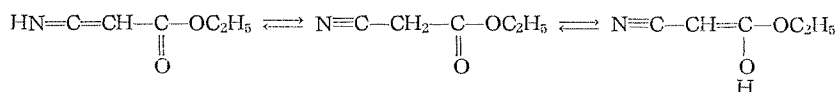
The enol content (0.01 %)<sup>34)</sup> of diethyl malonate is very small and this enol form has an intramolecular hydrogen bond (IX)<sub>4</sub>.<sup>35)</sup>

This hydrogen bond (IX)<sub>4</sub> is weaker than that of acetylacetone or ethyl acetoacetate, therefore the addition of pyridine causes fission of the hydrogen bond, giving an anion (X)<sub>4</sub> and a hydropyridinium ion (XI)<sub>4</sub>. In the reaction of ketene with these ions, the C-acetyl derivative of diethyl malonate (XIII)<sub>4</sub> is formed by the same mechanism as is seen in the reaction of ketene with the sodium salt of diethyl malonate.

With progress of the reaction, the keto form shifts to the enol form.



Two kinds of tautomerism,<sup>36)</sup> keto-enol and nitrile-ketenimide tautomerism, in ethyl cyanoacetate are as follows :



The atomic distance O $\cdots$ N in the enol form or the ketenimide form of ethyl

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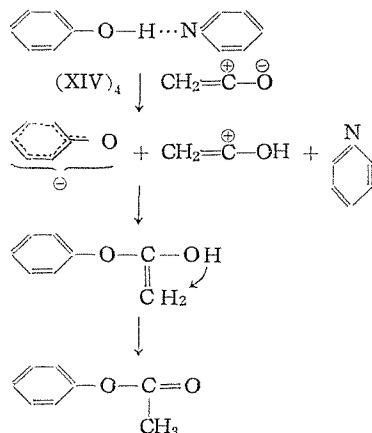
cyanoacetate is larger than 3 Å, on the other hand, the atomic distance O...N in the hydrogen bond N...H—O is 2.6 Å, so hydrogen bond does not exist in ethyl cyanoacetate.<sup>37)</sup> Therefore, when pyridine is added to ethyl cyanoacetate, the former takes a proton from hydroxy group of the enol form and the imino group of the ketenimide form of the latter, and the anion corresponding to (X)<sub>4</sub> are formed.

In the reaction of ketene with these ions, the C-acetyl derivative of ethyl cyanoacetate is formed by the same mechanism as is seen in the reaction of ketene with the sodium salt of ethyl cyanoacetate.

It can be supposed that in the mixture of pyridine and diethyl malonate or ethyl cyanoacetate, besides the above-mentioned hydropyridinium ion, the hydrogen bond between the active methylene group and pyridine (C—H...N<img alt="pyridine ring" data-bbox="750 355 805 385"/>) is also formed. But, as the ionization tendency of C—H is small (PK<sub>A</sub> ≅ 12.9), the hydrogen bond is not formed. Even if the hydrogen bond is formed and in the reaction of ketene with the compound corresponding to (I)<sub>4</sub>, the O-acetyl derivative is given by the same mechanism as the O-acetyl derivative of ethyl acetoacetate is formed, it cannot be detected because of its unstability as in the reaction in the presence of sulfuric acid. While, the N-acetyl derivative of ethyl cyanoacetate should be formed theoretically, but it could not be obtained because of its unstability or its very low yield.

Then, to explain the mechanism of reactions of ketene with phenols in the presence of pyridine, for example, the reaction of ketene with phenol will be considered.

In the mixture of phenol and pyridine, the hydrogen bond (XIV)<sub>4</sub> is formed. In the reaction of ketene with (XIV)<sub>4</sub>, the O-acetyl derivative of phenol is given by the same mechanism as is seen in the reaction of ketene with sodium salt of phenol. The above-mentioned mechanism is shown in the following formulas:



The O-acetyl derivatives of resorcinol, phloroglucinol and dimedone are formed



respectively by the same mechanism as the O-acetyl derivative of phenol is formed.

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